

CASE REPORT

Posterior Reversible Encephalopathy Syndrome and Anti-Angiogenic Agents: A Case Report

Filipe Manuel dos Reis Simões da Silva,¹ Peter Mike Burgos Pêgo,¹ Maria Cristina Henriques Vendrell,¹ Maria João de Azevedo Batalha Ferreira dos Santos Farias,¹ Ângela Cátia Ribeiro Timóteo,² Maria Cristina Martins da Costa,² Isabel Maria Monteiro Barbosa Moreira Cravo,³ and Fernando Manuel Ribeiro Gomes⁴

Departments of ¹Ophthalmology

²Neurology

³Neuroradiology

⁴Oncology, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

ABSTRACT

Posterior reversible encephalopathy syndrome is an increasingly recognised clinico-radiological entity, associated with several medical conditions (such as systemic arterial hypertension) and characterised by seizures, altered mental status, headaches, and visual symptoms. Magnetic resonance imaging is a key component in this diagnosis, with hyperintense foci in T₂-weighted images, corresponding to vasogenic oedema. The pathophysiology is not fully understood but probably involves loss of auto-regulation of cerebral vasculature or endothelial dysfunction or both. A 56-year-old male, suffering from a gastro-intestinal stromal tumour with hepatic metastasis resistant to imatinib, on therapy with sunitinib, came to the Emergency Department because of headaches, hallucinations, and loss of vision. There was no previous history of high blood pressure. A hypertensive crisis was diagnosed; ophthalmological examination on admission showed no light perception bilaterally. Brain imaging displayed bilateral parieto-occipital and frontal vasogenic oedema, consistent with the clinical diagnosis of posterior reversible encephalopathy syndrome. After treatment of hypertension and suspension of sunitinib, the patient recovered from his symptoms. Control imaging showed no oedema. Angiogenesis inhibitors, such as sunitinib and bevacizumab, can cause hypertension, one of the many medical conditions associated with the posterior reversible encephalopathy syndrome. This syndrome should be considered in cases of acute visual loss, particularly in view of its reversible nature when diagnosed and treated promptly.

KEYWORDS: bevacizumab; cortical blindness; posterior reversible encephalopathy syndrome; sunitinib; vasogenic oedema

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES), also named posterior reversible

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Correspondence: Filipe Manuel dos Reis Simões da Silva, MD,
 Department of Ophthalmology, Hospital Prof. Doutor Fernando
 Fonseca, IC 19-Venteira, 2720-276, Amadora, Portugal. E-mail:
 ssfilipe@gmail.com

leucoencephalopathy syndrome,¹ is an increasingly recognised clinical and radiological entity, first described in 1996 by Hinchey et al.²

Several medical conditions have been associated with this syndrome, such as systemic arterial hypertension (SAH), pre-eclampsia or eclampsia, renal dysfunction, several chemotherapeutic and immunosuppressant agents, systemic lupus erythematosus or solid organ transplantation,^{1,3–11} among others (Table 1).

The pathophysiology of this entity is not yet fully understood. The presence of vasogenic oedema is universal,^{1,3-8} but its origin remains controversial. The reversibility of the clinical and radiological changes seems to minimize the importance of cytotoxic

TABLE 1 Medical conditions associated with PRES^{3,5,6}.

Severe hypertension
Pre-eclampsia/eclampsia
Acute or chronic renal disease
Immunosuppressive drugs
Cyclosporine A
Tacrolimus (FK-506)
High-dose steroids
Interferon alpha
Chemotherapy agents
Cytarabine
Cisplatin
Gemcitabine
Vincristine
Tiazofurin
Bevacizumab
Sunitinib
Sorafenib
Combination chemotherapy (CHOP/CVP)
Other drugs
Intravenous immunoglobulin
Erythropoietin
Granulocyte stimulating factor
Interleukin
Antiretroviral therapy in HIV-infected patients
Infection/sepsis
Autoimmune diseases
Systemic lupus erythematosus
Systemic sclerosis
Wegener's granulomatosis
Polyarteritis nodosa
Thrombotic thrombocytopenic purpura
Haemolytic uraemic syndrome
Liver failure
Endocrine dysfunctions
Bone marrow transplantation
Solid organ transplantation
Blood transfusion
Tumour lysis syndrome
Hypercalcaemia/hyperparathyroidism
Hypomagnesaemia
Hypocholesterolaemia
Guillain-Barré syndrome
Porphyria
Contrast media exposure
Ephedra overdose
Cocaine or amphetamines abuse
Scorpion envenomation
Hydrogen peroxide

oedema in this syndrome, although there have been cases where both kinds of oedema coexist.^{6,12}

The most widely accepted theory is that severe SAH leads to loss of auto-regulation of the cerebral vasculature, with consequent hyperperfusion, endothelial cell injury, blood-brain barrier disruption, and formation of vasogenic oedema.¹³

Besides SAH, other contributing mechanisms have been put forward, such as endothelial dysfunction secondary to toxicity,^{2,6,13} as in cases of cytotoxic therapies, or a state of endothelial activation,^{3,13} as in eclampsia, sepsis, or tumour cell lysis after chemotherapy.

Whatever the implicated mechanisms, they all seem to be related to a dysfunction at the blood-brain barrier level.⁷ The posterior cerebral circulation is the most frequently affected,^{4,12} due to its relative lack of perivascular sympathetic innervation, rendering it more susceptible, as there is a more rapid loss of protective vasoconstriction.^{4,12,14,15}

The clinical picture is characterised by acute or subacute onset of headaches, altered mental status (including confusion, lethargy, somnolence, or even coma), seizures or visual symptoms,^{3,12,15} namely blurred vision, scotoma,⁷ hemianopia,⁵ visual hallucinations,⁷ visual neglect,⁵ or blindness.^{6,7} Other features, such as nausea, vomiting,¹⁰ paresis,¹² or other focal deficits may also be present.

Ophthalmic examination is almost always normal, although there may be signs of acute or chronic SAH, such as optic disc oedema, haemorrhages, or exudates.^{6,7}

Originally described as a subcortical disease of the posterior cerebrum,² with symmetrical changes in both parietal and occipital lobes, more recently published series have shown different radiological findings and patterns, such as cortical involvement, as well as frontal, temporal, or, less commonly, cerebellum, brainstem, or basal ganglia lesions.^{4,6,16} Although it occurs but rarely, a unilateral pattern of PRES may be found.⁷

Brain computed tomographic (CT) imaging may be useful as a first examination, exhibiting hypodense areas in susceptible regions, but the diagnosis is more firmly established using brain magnetic resonance imaging (MRI). T₂-weighted and fluid-attenuated inversion recovery (FLAIR) MRI images show cortical and subcortical hyperintensities²⁻⁸ corresponding to areas of vasogenic oedema. These can be distinguished from cytotoxic oedema with the more recent advances in MRI technology, such as diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps (elaborated from the diffusion data).

In DWI, vasogenic oedema has normal or decreased signal intensity, differentiating it from cytotoxic oedema, with increased signal.^{8,12} In the same way, ADC maps allow distinction between both kinds of

oedema, with vasogenic oedema showing increased signal and decreased signal in cases of cytotoxicity.^{8,12}

Since DWI has signal contributions from both underlying T_2 weighting as well as diffusion weighting, hyperintensities in this sequence may be due to true diffusion restriction (such as infarction) or strong T_2 effects, the so-called shine-through effect. ADC maps are very useful in these particular cases, allowing distinction between vasogenic oedema, with a bright appearance, and cytotoxic oedema or true infarction, with a low signal; this feature may play an important role in predicting the final outcome of this condition.¹²

The differential diagnosis of PRES includes a wide spectrum of neurological diseases, such as ischaemic stroke, infectious encephalitis, cerebral venous thrombosis, central nervous system (CNS) vasculitis, or CNS neoplasm (especially if unilateral).^{4,5}

Most of the cases are completely reversible with control of SAH or removal of the inciting agent. If the causative factor is not promptly withdrawn, it may lead to ischaemia or haemorrhage and subsequent permanent neurological deficits or epilepsy.^{1,7,15}

MATERIALS AND METHODS

We report a single case of PRES following therapy with sunitinib.

The patient was assessed by an interdisciplinary team of ophthalmologists, neurologists, a neuroradiologist and an oncologist; an extensive investigation included brain CT scans and MRI and a Goldmann visual field test.

RESULTS

A 56-year-old Caucasian male experienced simple visual hallucinations for 3 hours, followed by acute bilateral painless loss of vision. On clinical interrogation he complained of mild occipital bilateral headaches for the previous 3 weeks.

Past medical history included a gastro-intestinal stromal tumour (GIST) diagnosed 12 years before, with hepatic metastasis for the last 3 years. The patient had undergone multiple surgical interventions and chemotherapy cycles, including imatinib for 5 years, to which the disease had gained resistance. He was on the 4th week of his second cycle of oral therapy with 50 mg/day of sunitinib (regimen 4 weeks on, 2 weeks off), an anti-angiogenic agent. He had completed his first treatment 6 weeks before, without any complications. He had no other known diseases, specifically no SAH. Usual medication, besides chemotherapy, included domperidone and omeprazole.

On admission, ophthalmological assessment showed no light perception (NLP) in both eyes, preservation of the pupillary reflexes and normal funduscopic examination, with no other changes. Physical examination revealed a blood pressure (BP) elevated at 210/114 mm Hg, with the rest of the clinical examination being normal.

Emergent brain CT scan revealed bilateral parieto-occipital hypodense lesions, possibly related to oedema (Figure 1), and the patient was admitted with the presumptive diagnosis of PRES.

After prompt institution of BP-lowering therapy (captopril, furosemide, and amlodipine), BP was normalised by the 3rd day; on that same day he began to recover his vision, with a visual acuity of 6/10 OU. Concurrently, he started experiencing complex visual hallucinations and palinopsia.

On the 4th day, treatment with sunitinib was suspended, thus completing the scheduled course; on the same day, a brain MRI was performed, which confirmed the diagnosis of PRES. T_2 FLAIR images showed cortical and subcortical bilateral oedematous lesions in parieto-occipital regions, as well as in both frontal white and grey matter, more evident on the right side (Figures 2 and 3A). In order to better characterise the oedema, DWI was obtained (Figure 3B), showing increased signal in the parieto-occipital lobes, which was no more

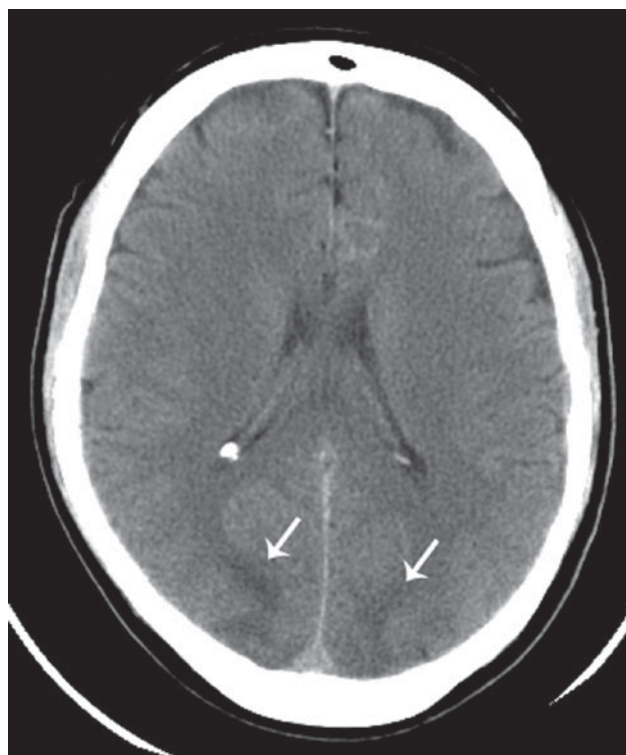


FIGURE 1 Brain computed tomographic scan, 1st day: parieto-occipital hypodense lesions, suggestive of oedema (white arrows).

than the shine-through effect, as shown by the ADC map, displaying hyperintensities in the posterior lobes (Figure 3C). These findings pointed to a vasogenic type of oedema, predicting a good outcome.

During hospitalisation, ophthalmological examination was completely normal, namely the pupillary reflexes and the fundus examination.

Visually evoked potentials were normal.

The patient left the hospital on the 8th day, with an uncorrected visual acuity of 10/10 but still experiencing visual hallucinations and palinopsia. These disappeared progressively over the following 5 weeks. BP values were normal on discharge from hospital and the patient was left without anti-hypertensive medication.

A control brain MRI, performed 6 weeks later, showed complete resolution of the lesions (Figure 4). Clinical examination (namely ophthalmic and neurological examinations) and a Goldmann visual field test later performed showed no permanent deficits.

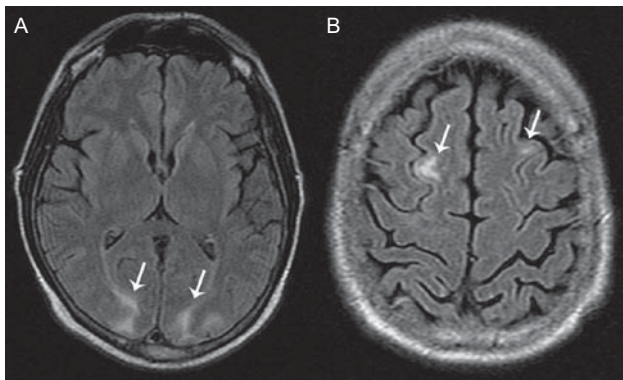


FIGURE 2 Brain MRI, 5th day: FLAIR images showing cortical and subcortical bilateral parieto-occipital (A) and frontal lesions (B) (white arrows), corresponding to oedema.

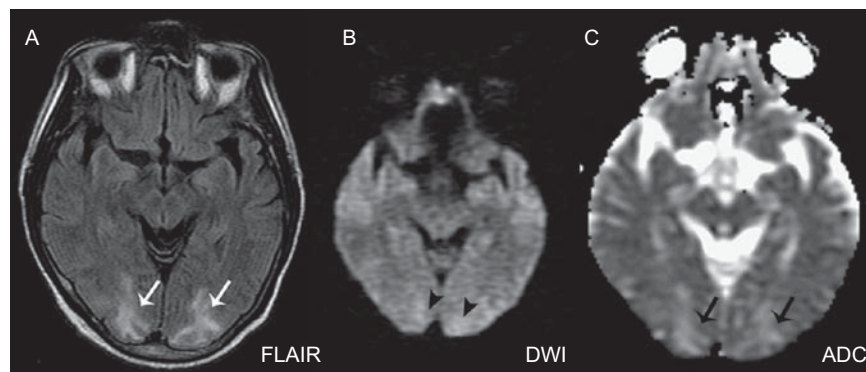


FIGURE 3 Brain MRI, 5th day. (A-) FLAIR: Hyperintense lesions in the posterior lobes, corresponding to oedema (white arrows). (B-) DWI: Discrete hyperintensities in the posterior lobes (black arrow heads), corresponding either to shine-through effect or true diffusion restriction. (C-) ADC: Increased hyperintensity in the posterior lobes (black arrows), corresponding to vasogenic oedema.

DISCUSSION

Sunitinib is a tyrosine-kinase (TK) inhibitor; its anti-angiogenic activity is mediated by inhibition of the vascular endothelial growth factor (VEGF) TK receptor, among other TK receptors.¹⁷ It is used mainly in renal cell carcinoma and GIST, especially when there is metastatic disease.¹⁷ Other TK inhibitors in clinical use include drugs such as sorafenib, erlotinib, gefitinib, lapatinib, nilotinib, and dasatinib.

Bevacizumab, a monoclonal antibody, has also an anti-angiogenic activity but through a different mechanism: by binding VEGF, it prevents its interaction with its receptors (Flt-1 [VEGFR1] and KDR [kinase insert domain receptor; VEGFR2]) on the endothelial cells surface, thereby preventing the formation of new blood vessels.

Despite being generally well tolerated, angiogenesis inhibitors may be associated with SAH. The exact mechanism by which this occurs is not yet fully understood, although vascular rarefaction, endothelial dysfunction, or altered nitrous oxide metabolism have been suggested.¹⁷

We present a case of a patient with no known SAH, who was admitted with visual symptoms (visual hallucinations and blindness), headaches, and a hypertensive crisis. This clinical picture manifested on the 4th week of his second treatment cycle with sunitinib, after having gained resistance to treatment with imatinib.

MRI images showed typical signs of PRES, with lesions affecting both cortical and subcortical tissues, and involving occipital, parietal, and frontal lobes bilaterally; ADC confirmed the vasogenic nature of the oedema, the lesions being hyperintense. Repeated neuroimaging showed complete resolution of the oedema, accounting for the reversibility of this syndrome.

Although sunitinib was suspended only 4 days after his admission, clinical recovery began on the 3rd day, with improvement in visual acuity (from NLP in both eyes to 6/10 OU) following an aggressive anti-hypertensive therapy. This fact supports the theory that SAH, rather than the drug itself and its possible direct action on the endothelial cells, was the main cause for the loss of vascular auto-regulation of the cerebral circulation, leading to vasogenic oedema.

As stated before, several mechanisms may coexist in PRES; in this particular case, besides SAH associated with a hyperperfusion state and endothelial toxicity caused by the drug, one may also speculate whether tumour cell lysis could be a contributing factor.

It is questionable whether the patient should have stopped treatment with sunitinib as soon as the diagnosis of PRES was put forward. After discussion of the patient's condition with the oncologist and since the putative trigger of PRES in this case was the abnormally high blood pressure, a decision was made to

complete the 4-week plan of sunitinib treatment, along with treatment of the hypertension.

One question remains unanswered, however: why did this occur at this point of treatment, since 6 weeks before the patient had completed the same plan without any complications? We can offer no explanation for this fact, although it is known that SAH may develop either with drug initiation or within the first year of treatment with anti-angiogenics.¹⁸

Three other cases of PRES associated with sunitinib have been described^{19–21} (Table 2), all of them in the context of renal cell carcinomas (which had metastasised to bone, liver and lung, and ovaries, respectively). As with our patient, there was no previous history of SAH and all cases had a complete recovery, both clinically and radiologically. The clinical picture was somewhat different, with partial seizures in one patient, confusion in the second one, and headaches and generalised seizures in the third case. The delay of symptom onset ranged from 1 week to 5 months. The presented case is the first report of PRES associated with sunitinib presenting with cortical visual loss rather than seizures, altered mental status or headache.

Reports of PRES associated with bevacizumab^{22–28} (Table 2) have been published, all of them with complete or partial resolution.

Sorafenib, another anti-angiogenic drug, has also been implicated in cases of PRES^{29,30} (Table 2).

PRES should be considered in all cases of acute cerebral visual loss. Ophthalmologists should be aware that they may be the first physicians to examine PRES patients and that early diagnosis and treatment may be crucial to the reversibility of this process.

In addition, recognizing this syndrome and differentiating it from acute cerebral ischaemia, in the appropriate clinical context (acute hypertension, chemotherapy, eclampsia) described above, may prevent institution

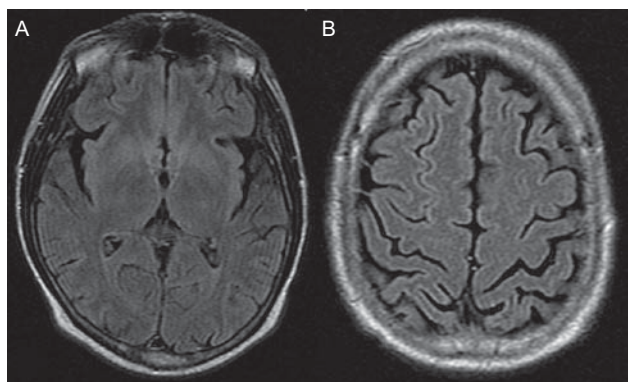


FIGURE 4 MRI, 6th week: FLAIR images showing complete resolution of the oedema, both parieto-occipital (A) and frontal (B).

TABLE 2 Cases of PRES associated with anti-angiogenics^{19–30}.

Reference	Anti-angiogenic drug	Age/sex	Underlying disease	Previous history of hypertension
Martin <i>et al.</i> (2007) ¹⁹	Sunitinib	70/F	Metastatic renal cell carcinoma	No
Medioni <i>et al.</i> (2007) ²⁰	Sunitinib	81/F	Metastatic renal cell carcinoma	No
Cumurcic <i>et al.</i> (2008) ²¹	Sunitinib	39/F	Metastatic renal cell carcinoma	No
Glusker <i>et al.</i> (2006) ²²	Bevacizumab	52/F	Metastatic renal cancer	No
Ozcan <i>et al.</i> (2006) ²³	Bevacizumab	59/F	Metastatic rectal adenocarcinoma	No
Jeffrey <i>et al.</i> (2006) ²⁴	Bevacizumab	52/M	Rectal carcinoma	No
Kapiteijn <i>et al.</i> (2007) ²⁵	Bevacizumab	54/F	Gastrointestinal stromal tumor	Yes
Levy <i>et al.</i> (2008) ²⁶	Bevacizumab	6/F	Hepatoblastoma	No
Maalouf <i>et al.</i> (2008) ²⁷	Bevacizumab	55/F	Metastatic colon cancer	No
Koopman <i>et al.</i> (2008) ²⁸	Bevacizumab	49/M	Colorectal cancer	No
Govindarajan <i>et al.</i> (2006) ²⁹	Sorafenib	49/F	Cholangiocarcinoma	No
Dogan <i>et al.</i> (2009) ³⁰	Sorafenib	58/M	Hepatocellular carcinoma	No

of potentially dangerous invasive procedures, such as thrombolytic therapy.

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